PATENT
2503-1186

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Ezio BOMBARDELLI — Conf. 5416

Application No. 10/562,205 — Group 1655

Filed May 15, 2006 — Examiner Catheryne Chen

FORMULATIONS FOR THE TREATMENT
OF ARTHRITIS CONDITIONS

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

April 1, 2008

Applicants request a pre-appeal brief review of the final rejection in the above-identified application. No amendments are being filed with this request.

A Notice of Appeal is filed herewith.

The review is requested for the reasons advanced on the attached sheets.

Respectfully submitted,

YOUNG & THOMPSON

Robert A. Madsen Reg. No. 58,543
209 Madison Street
Suite 500
Alexandria, VA 22314
Telephone (703) 521-2297
Telefax (703) 685-0573
(703) 979-4709

RM/mjr

REASONS IN SUPPORT OF REQUEST FOR REVIEW

Claims 1-4 are not rendered obvious by CHRUBASIK et al. 1998 ("CHRUBASIK"), TAMEJA et al. US 5,629,351 ("TAMEJA"), CHARTERS et al. US 6,541,045 ("CHARTERS"), KEMPER, and LOCKHOFF et al. US 4,710,491 ("LOCKHOFF").

The position of the Official Action is that the ingredients of the publications treat diseases that "are inflammation related ailments, which are painful. Thus, it would be obvious to combine them to treat pain."

However, the proposed combination cannot render obvious the claimed invention for at least three reasons:

(I) The combination fails to teach glucuronic acid or glucuronolactone.

The Official Action combines the ingredients from the publications to treat inflammation related ailments.

LOCKHOFF, in particular, is offered for teaching an "anti-arthritic compound of 15 g of D-glucuronolactone".

However, the 15 g of D-glucuronolactone are not part of an anti-arthritic compound.

Rather, the 15 g of D-glucuronolactone are part of a reaction that forms an anti-arthritic compound. Methyl glucuronate is formed from the 15g of D-glucuronolactone, and the methyl glucuronate is reacted and worked up to form N-

Glucopyranosyl-N-octadecyl-oleic acid amide. See, e.g., example 30, column 11, lines 1-14.

Indeed, the focus of LOCKHOFF is to administer N-glycosylated carboxylic acid derivatives to treat rheumatic diseases.

Thus, the proposed combination cannot teach the composition according to independent claim 1, as N-glycosylated carboxylic acid derivatives, not glucuronic acid, nor glucuronolactone, treat inflammation ailments.

(II) There is no reason to combine the ingredients as proposed.

As discussed above in reason (I), D-glucuronolactone is used to produce methyl glucuronate, and the methyl glucuronate is reacted and worked up to form an anti-arthritic compound.

Accordingly, based on LOCKHOFF, one of ordinary skill in the art would have been strongly discouraged from selecting a D-glucuronolactone to treat any inflammation ailment, as it is merely a reactant used in the production of an anti-arthritic compound.

The Official Action fails to provide any reasoning for selecting a reactant instead of the active compound.

(III) None of the publications suggests the synergistic effects obtained by the claimed invention.

The declaration filed July 13, 2007 demonstrates that the compounds have a synergistic effect when administered in combination for treating patients suffering from osteoarthritis of the knee. See, e.g., Tables 1-3 of the declaration.

The position of the Official Action is that the data shows an additive effect, and "[w]hen the standard deviations are considered, there really is significant difference".

To show that data demonstrates synergism, the pain data and the stiffness data from the declaration were analyzed according to the Bürgi formula, which is a universally accepted formula in pharmacology (See Acta Pharmacol Sin 2004 Feb; 25(2): 146-147, in the appendix of the response filed February 5, 2008):

q=observed value/expected value (the Bürgi formula)
with a tolerance of ±0.15
where:
q=1 represents simple addition (i.e. additive effect)
q>1 represents synergism or potentiation
q<1 represents antagonism.

The expected value is the sum of the individual effects exerted by each compound, e.g., as administered to patient Groups 2-6. The individual effects are calculated as the difference between Day 0 and Day 14 values in Tables 1 and 2 below:

TABLE 1: Expected Value for Pain

Group	Effect
2	43.6 - 37.3= 6.3
3	43.7 - 37.3 = 4.6
4	43.5 - 41.1 = 2.4
5	45.1 - 42.8 = 2.3
6	44.9 - 44.5 = 0.4
Expected value for Pain	6.3 + 4.6 + 2.4 + 2.3 + 0.4 = **15**

TABLE 2: Expected Value for Stiffness

Group	Effect
2	42.4 - 44.1= -1.7
3	41.9 - 35.3 = 6.7
4	40.3 - 39.1 = 1.2
5	41.2 - 40.8 = 0.4
6	42.7 - 42.5 = 0.2
Expected value for Stiffness	-1.7 + 6.7 + 5.8 + 1.2 + 0.4 + 0.2 = **12.6**

The observed value is the effect of the combination of compounds, e.g., as administered to patient Group 7, which is calculated as the difference between the values from Day 0 and Day 14 in Tables 3 and 4:

TABLE 3: Observed Value for Pain (Group 7)
43.8 - 25.3 = **18.5**

TABLE 4: Observed Value for Stiffness (Group 7)
42.8 - 23.2 = **19.6**

Thus, parameter "q" based on Tables 1-4 above is:

q for Pain	q for Stiffness
18.5/15 = **1.23**	19.6/12.6 = **1.55**

As q is greater than 1, the compounds administered separately for Groups 2-6, i.e., Salix rubra extract, Boswellia serrata exact, Green tea extract, N-acetyl, glucosamine and Glucuronolactone, behave synergistically when administered together for Group 7, e.g., the claimed invention.

The standard deviation further suggests that the compounds exert a synergist effect. The difference in values between Day 0 and Day 14 in Groups 4, 5, and 6 are not statistically significant. That is, each single active compound fails to exert a significant effect on both pain and stiffness in the Day 0 to Day 14 period. The values for Group 7, however, are statistically significant for the same period.

Thus, the increased effect observed for Group 7 is attributed to the synergism of the five active compounds.

The Official Action also states that Boswellia extract "senolee" of the declaration is not claimed. However, applicant respectfully submits that this is a typographical error, and that Boswellia extract serrata was actually evaluated.

Therefore, the proposed combination fails to render obvious independent claim 1, and dependent claims 2-4.

Claims 1-5, 7-8 are not rendered obvious by CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and LOCKHOFF, further in view of CHEN et al. US 2002/0032171A1 ("CHEN") and BELCH et al. ("BELCH").

CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and LOCKHOFF are offered for the reasons discussed above.

CHEN and BELCH are offered for teaching Oenothera biennis oil for rheumatologic conditions. However, neither of these publications suggests glucuronic acid or glucuronolactone to "treat inflammation related ailments", and, thus, they cannot remedy the deficiencies of CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and LOCKHOFF for reference purposes.

Therefore, the proposed combination fails to render obvious independent claim 1, and dependent claims 2-5 and 7-8.

Conclusion

As shown above, the rejections of record include clear factual and/or legal errors and should be withdrawn and this application allowed, and such is respectfully requested.